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### **Suspected anaphylaxis after intravenous administration of cefuroxime (Zinacef) in two dogs, with descriptions of arterial blood gas abnormalities over time**

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# VetRecordCaseReports

## Suspected anaphylaxis after intravenous administration of cefuroxime (Zinacef) in two dogs, with descriptions of arterial blood gas abnormalities over time.

Journal:	<i>Veterinary Record Case Reports</i>
Manuscript ID	vetreccr-2019-000922.R1
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Keywords:	Dogs, Anaesthesia, Antimicrobials, Allergy
Topics:	Anaesthesia and analgesia, Immunology (including allergy), Emergency medicine and critical care
Abstract:	Two cases of suspected anaphylaxis occurred in our hospital within 2 weeks of each other. The first, a 6-year 4-month-old Border Collie presented for thoracic wall resection. Once anaesthetised, 20mg/kg of intravenous cefuroxime (Zinacef 75mg/ml, GlaxoSmithKline UK, UK) was administered slowly for prophylactic antibiotics. Ten minutes after administration was completed – desaturation occurred alongside tachycardia, hypotension, and apnoea. Chest compliance was extremely poor, with minimal chest movement. Treatment included intermittent positive pressure ventilation, intravenous fluids, terbutaline, adrenaline, and dexamethasone. The second case, a 5-year 8-month old Lhasa Apso presented for elective orthopaedic surgery. Intravenous cefuroxime (Zinacef 75mg/ml, GlaxoSmithKline UK, UK) was again administered slowly for prophylactic antibiotics; however, it is uncertain whether the patient received the full dose of 20mg/kg. Mid administration tachycardia, tachypnoea, and hypotension occurred – alongside poor chest compliance. Cefuroxime administration was stopped, the fluid line disconnected and treatment with chlorphenamine given.

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# Veterinary Record casereports

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### **TITLE OF CASE** *Do not include "a case report"*

Suspected anaphylaxis after intravenous administration of cefuroxime (Zinacef) in two dogs, with descriptions of arterial blood gas abnormalities over time.

### **SUMMARY** *Up to 150 words summarising the case presentation and outcome (this will be freely available online)*

Two cases of suspected anaphylaxis occurred in our hospital within 2 weeks of each other. The first, a 6-year 4-month-old Border Collie presented for thoracic wall resection. Once anaesthetised, 20mg/kg of intravenous cefuroxime (Zinacef 75mg/ml, GlaxoSmithKline UK, UK) was administered slowly for prophylactic antibiosis. Ten minutes after administration was completed – desaturation occurred alongside tachycardia, hypotension and apnoea. Chest compliance was extremely poor, with minimal chest movement. Treatment included intermittent positive pressure ventilation, intravenous fluids, terbutaline, adrenaline and dexamethasone. The second case, a 5-year 8-month old Lhasa Apso presented for elective orthopaedic surgery. Intravenous cefuroxime (Zinacef 75mg/ml, GlaxoSmithKline UK, UK) was again administered slowly for prophylactic antibiosis; however, it is uncertain whether the patient received the full dose of 20mg/kg. Mid administration tachycardia, tachypnoea and hypotension occurred – alongside poor chest compliance. Cefuroxime administration was stopped, the fluid line disconnected and treatment with chlorphenamine given.

### **BACKGROUND** *Why you think this case is important – why did you write it up?*

Anaphylaxis is a rare but potentially life threatening adverse event, and can occur in response to many commonly administered perioperative medications (1). A recent human national audit in the United Kingdom reported an incidence of perioperative anaphylaxis of 1 in 10,000 anaesthetics, with the most common triggers being intravenous (IV) antibiotics (47%) and muscle relaxants (33%) (2). In veterinary patients, incidence of perioperative anaphylaxis is unknown. Numbers of reports of drug related anaphylaxis in the veterinary literature are small, reported suspected triggers include IV antibiotics(3-6), IV contrast agents (7, 8) IV buprenorphine (9), IV propofol emulsion (10), thiopentone (11, 12) and rocuronium (13). These are summarised in table 1. Due to the low number of reports of

perioperative anaphylaxis in veterinary medicine, we felt it was imperative to document these cases. This is the first detailed report of suspected anaphylaxis following administration of cefuroxime (Zinacef, GlaxoSmithKline) in two dogs. We hope this will raise awareness of the possibility of anaphylaxis under general anaesthesia, especially with a commonly used drug that may potentially be considered a safer choice than other intravenous antibiotics such as amoxicillin clavulanate (Augmentin, GlaxoSmithKline) (4) due to the current ratio of reports in the veterinary literature.

#### **CASE PRESENTATION** *Presenting features, clinical and environmental history*

Case 1: A six-year four-month old female neutered Border Collie weighing 19.8 kg presented for right thoracic wall and rib resection. Diagnostic CT imaging under general anaesthesia undertaken 6 days prior to surgery confirmed the presence of a soft tissue mass invading the twelfth and thirteenth intercostal spaces on the right side. No evidence of metastasis was seen. The dog was not on any current medication, and no other medical concerns were reported. Blood work (haematology, biochemistry and electrolytes) taken 6 days prior to surgery revealed mild elevations in glucose (5.6mmol/L; ref 3-5mmol/L), cholesterol (7.9mmol/L; ref 3.8-7mmol/L), and alkaline phosphatase (75U/L; ref 20-60U/L). All other results were within normal limits. On pre-anaesthetic examination, body condition score was deemed to be 7/9. Auscultation of the chest was unremarkable, no cardiac murmurs or arrhythmias detected and normal lung sounds audible bilaterally. The patient was panting, heart rate was 120 beats per minute with a synchronous metatarsal pulse, capillary refill time (CRT) was less than two seconds, and mucous membranes were pink. Pre-medication with 0.2mg/kg methadone (Comfortan 10mg/ml, Dechra Veterinary Products, UK) and 3mcg/kg dexmedetomidine (Dexdomitor 0.5mg/ml, Vetoquinol UK Ltd, UK) was administered intramuscularly, and twenty minutes later an intravenous catheter placed in the right cephalic vein. Anaesthesia was induced with propofol to effect (PropoFlo Plus 10mg/ml, Zoetis UK Ltd, UK), which totalled 38mg (1.9mg/kg). The trachea was intubated with a cuffed size 10.5mm endotracheal tube, and connected to a circle breathing system. Anaesthesia was maintained with isoflurane (IsoFlo 100%, Zoetis UK Ltd, UK) in oxygen, at a percentage required to provide suitable anaesthetic depth. A multi-parameter monitor (Datex-Ohmeda S/5 Compact) was used for anaesthetic monitoring which included ECG, pulse oximetry, capnography, and oscillometric blood pressure measurement (NIBP). Intravenous fluid therapy was started (Vetivex 11/Hartmanns, Dechra Veterinary Products, UK) at 4ml/kg/hr, and clipping of the surgical site began. Intravenous cefuroxime (Zinacef 75mg/ml, GlaxoSmithKline UK, UK) at a dose of 20mg/kg was administered over ten minutes for prophylactic antibiosis. Immediately prior to the start of antibiotic administration HR was 55 beats per minute, respiratory rate 6 breaths per minute, mean arterial pressure 72mmHg, SpO<sub>2</sub> 97% and ET CO<sub>2</sub> 51mmHg. An arterial line was placed in the left dorsal pedal artery for invasive blood pressure measurement, and for arterial blood gas sampling. A blood sample was collected for baseline packed cell volume and total protein prior to surgery (45% and 68g/L respectively) and for blood typing if required. Ten minutes after completion of cefuroxime administration, apnoea was noted. This was initially managed with intermittent manual ventilation, however desaturation quickly followed with SpO<sub>2</sub> falling to from 98% to 85% within 2 minutes. At this stage when manual ventilation was attempted, chest compliance was poor with minimal chest movement and no capnograph trace. Heart rate had increased from 55 beats per minute to 165 beats per minute, and oscillometric blood pressure, which had been reliably cycling at 5-minute intervals, was no longer reading. Manual ventilation continued, and although chest compliance still felt poor, a capnograph trace was visible after 8-10 breaths, showing a prolonged expiratory upstroke with EtCO<sub>2</sub> of 60-80mmHg. Oxygen saturation improved with manual ventilation, with SpO<sub>2</sub> increasing to 100%. Mucous membranes were dark pink in colour with CRT of 1 second. The first NIBP reading registered after the event was 10 minutes after the onset of clinical signs and gave MAP of 48 mmHg. This increased to and remained above 60 mmHg after treatment as described later.

Case 2: A five-year eight-month old female neutered Lhasa Apso weighing 7.9 kg presented for an elective surgical management of medial patella luxation. On pre-anaesthetic examination auscultation of the chest was unremarkable, with no cardiac murmurs or arrhythmias detected and normal lung sounds present bilaterally. Respiratory rate was 16 breaths per minute and heart rate 88 beats per minute with synchronous good quality

pulses. Pre-medication with 0.2mg/kg methadone (Comfortan 10mg/ml, Dechra Veterinary Products, UK) and 10 mcg/kg acepromazine (Acecare 2mg/ml, Animalcare Limited, UK) was administered intravenously followed by induction of anaesthesia with propofol to effect (PropoFlo Plus 10mg/ml, Zoetis UK Ltd, UK), which totalled 36mg (4.5mg/kg). The trachea was intubated with a cuffed size 6mm endotracheal tube, and connected to a circle breathing system. Anaesthesia was maintained with isoflurane (IsoFlo 100%, Zoetis UK Ltd, UK) in oxygen, at a percentage required to provide suitable anaesthetic depth. A multi-parameter monitor (Datex-Ohmeda S/5 Compact) was used for anaesthetic monitoring as described previously. Intravenous fluid therapy was commenced (Vetivex 11/Hartmanns, Dechra Veterinary Products, UK) at 3ml/kg/hr, and clipping of the surgical site began. Intravenous cefuroxime (Zinacef 75mg/ml, GlaxoSmithKline UK, UK) at a dose of 20mg/kg was administered into the IV injection port of the giving set over twenty minutes for prophylactic antibiosis. Approximately ten minutes after cefuroxime had started to be administered, the respiration pattern changed to become shallow and rapid. Heart rate increased from 90 to 185 beats per minute, chest compliance was subjectively poor, and NIBP recorded MAP of 45 mmHg. At this point antibiotic administration was stopped, and the giving set disconnected from the patient and flushed through to remove any residual cefuroxime in the line. It was estimated the patient received approximately 10mg/kg of cefuroxime (half of the prescribed dose).

## **INVESTIGATIONS *If relevant***

Case 1: Tracheal intubation was visually confirmed to rule out inadvertent extubation, and a positive glide sign seen on thoracic ultrasound ruled out pneumothorax. Three arterial blood gas samples were taken; these are presented in table 2. Sample A, taken twenty minutes after cefuroxime administration and immediately after terbutaline administration shows a marked mixed acidosis with a pH of 7.12. The most likely cause would be hypercapnia due to alveolar hypoventilation, and significantly reduced oxygen delivery potentially causing lactic acidosis. The A-a O<sub>2</sub> gradient was high (309.7mmHg), with normal values in dogs expected to be less than 30mmHg when breathing room air (14) and less than 45mmHg in humans breathing 100% oxygen (15). Possible causes for this include ventilation perfusion (V/Q) mismatch, diffusion defect, or right to left shunting of blood. In this case, the most likely would be V/Q mismatch due to bronchoconstriction. Sample B, taken twenty minutes after sample A and following administration of adrenaline shows only mild improvement in acidosis and hypercapnia; however, the A-a O<sub>2</sub> gradient was significantly improved along with PaO<sub>2</sub>. Such an improvement could be explained by rapid alleviation of severe bronchoconstriction by adrenaline (or a delayed action of terbutaline), reducing V/Q mismatch. Sample C was taken 45 minutes after extubation, and approximately 1.5 hours post cefuroxime administration. The pH had returned to normal due to compensatory mechanisms for metabolic acidosis resulting in a low CO<sub>2</sub> and low HCO<sub>3</sub>. The A-a O<sub>2</sub> gradient had also normalised, however interestingly the patient was now hypokalaemic (K<sup>+</sup> 2.8mmol/L). It is possible that this hypokalaemia could have been caused by beta-2 adrenergic agonism of terbutaline and epinephrine.

## **DIFFERENTIAL DIAGNOSIS *If relevant***

Case 1: Once inadvertent endotracheal tube displacement or obstruction had been ruled out, a thoracic ultrasound ruled out pneumothorax. The ultrasound machine was set up in preparation for an ultrasound-guided nerve block so was the most rapid method of diagnosis as opposed to thoracic radiographs or thoracentesis. Bronchospasm – either idiopathic, due to underlying respiratory disease, or anaphylactic were the remaining differentials. With the presence of both respiratory and cardiovascular signs, anaphylaxis was suspected and treatment initiated.

## **TREATMENT *If relevant***

Case 1: Treatment initially consisted of initiation of manual intermittent positive pressure ventilation, and 10ml/kg of intravenous fluids (Vetivex 11/Hartmanns, Dechra Veterinary Products, UK) administered over ten minutes. Terbutaline 0.01mg/kg (Bricanyl 0.5mg/ml, AstraZeneca UK Ltd, UK) was administered intramuscularly once bronchoconstriction was suspected. Oxygen saturation increased to 100%; however no response was seen in terms



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of thoracic compliance. Therefore, five minutes later 0.005mg/kg of adrenaline (Adrenaline (epinephrine) 1 in 1000, Hameln pharmaceuticals ltd, UK) diluted in 1ml of fluids (Vetivex 11/Hartmanns, Dechra Veterinary Products, UK) was administered intravenously over 2 minutes. Immediately after adrenaline administration thoracic compliance was vastly improved and subjectively back to baseline levels. Dexamethasone 0.2mg/kg (Colvasone 0.2%, Norbrook Laboratories Ltd, UK) was administered intravenously prior to recovery from anaesthesia in an attempt to reduce the risk of a biphasic reaction, however evidence for this is still unclear (16). Potassium (Potassium chloride concentrate 15%, Hameln pharmaceuticals ltd, UK) was supplemented in intravenous fluids (Vetivex 11/Hartmanns, Dechra Veterinary Products, UK) until normokalaemia was restored.

Case 2: In the second case treatment consisted of 4mg chlorphenamine IV (Chlorphenamine maleate 10mg/ml, Wockhardt UK Ltd, UK), after which chest compliance subjectively returned to baseline levels, HR reduced to 75 beats per minute and MAP increased to 85 mmHg. The respiratory rate remained elevated at 25-30 breaths per minute so intermittent positive pressure ventilation was initiated. Desaturation did not occur in this case, and due to improvement of clinical signs – surgery proceeded.

**OUTCOME AND FOLLOW-UP**

Case 1: Approximately 40 minutes after initial clinical signs were seen, the patient passed a large amount of mucoid diarrhoea with fresh blood present. This was suspected to be a consequence of anaphylaxis due to the direct effect of histamine on the gastrointestinal mucosa, with diarrhoea being one of the symptoms listed on the World Allergy Organisation (WAO) grading system (17). At this point concern over pulmonary function was discussed between the anaesthesia and surgical teams. The A-a O<sub>2</sub> gradient was still very abnormal, and with the planned thoracic wall resection likely to compromise pulmonary gas exchange further, the decision was made to postpone the elective procedure. Upon removal of the endotracheal tube, a small amount of pink coloured fluid of slightly foamy consistency was noted at the distal end of the tube. The patient recovered uneventfully from general anaesthesia, and stayed in ICU overnight for close monitoring. The arterial catheter was left in place for further arterial samples to be taken as necessary and sample C taken 45 minutes post extubation shows a normal A-a O<sub>2</sub> gradient.

The dog was anaesthetised the following day for the planned thoracic wall resection, and no adverse events occurred. The anaesthetic protocol is detailed in table 3. Differences included 7mg of chlorphenamine (Chlorphenamine maleate 10mg/ml, Wockhardt UK Ltd, UK) given intravenously prior to premedication, and 2mg/kg of marbofloxacin (Marbocyl 200mg powder and solvent for injection, Vetoquinol UK Ltd, UK) as prophylactic antibiosis.

Case 2: Subjectively the patient required higher doses of analgesics to maintain an appropriate depth of anaesthesia, otherwise the rest of anaesthesia and recovery was uneventful.

**DISCUSSION *Include a very brief review of similar published cases***

This is the first case report to describe anaphylaxis from cefuroxime administration in dogs, and only the second in the veterinary literature of an adverse reaction. Anaphylaxis can be described as immunologic (immune complex or complement mediated) or non-immunologic (direct mast cell or basophil degranulation) (18, 19). Previously classification included types I, II, III (known respectively as anaphylactic, cytotoxic, immune complex) and type IV or delayed cell mediated hypersensitivity. However, pathophysiology is complex and clinically they are indistinguishable. Both immunologic and non-immunologic anaphylaxis result in systemic clinical signs including severe bronchospasm, laryngeal oedema, respiratory failure, hypotension and cardiovascular collapse (17). No evidence of previous administration of IV cefuroxime or oral cephalosporin could be found on the referring vet history for either patient, making a non-immunologic reaction most likely. The cases we describe meets these specifications, and using the World Allergy Organisation (WAO) grading scale (table 4) the first case would be graded as “5c; severe bronchospasm; 10 minutes” and the second case “5z; tachypnoea; 10 minutes”. Treatment is symptomatic, and varies with severity of clinical signs (20, 21). Due to lack of clinical trials in animals, these treatment options have been taken from human medicine (18, 19, 22), which include epinephrine, intravenous fluid resuscitation, supplemental oxygen and cardiopulmonary support. Antihistamines and

glucocorticoids are not advised as first line treatments for anaphylaxis in human medicine due to lack of evidence of benefit (22, 23).

The cases we describe here were managed differently from one another, and in part from the human guidelines above. Case 1 initially received terbutaline due to the presenting sign of bronchospasm – however despite seeing an improvement in oxygen saturation, chest compliance remained poor and adrenaline was administered slowly IV 5 minutes later. If an improvement in oxygen saturation had not been evident quickly, the decision to give adrenaline would have been made earlier – as it is key in these situations to not delay further therapy if the patient continues to deteriorate. With hindsight, adrenaline would have been the first line treatment of choice in this patient, although its use is not without risk. Adrenaline administration IV has a multitude of systemic effects due to actions on the  $\alpha_1$ ,  $\alpha_2$ ,  $\beta_1$  and  $\beta_2$  receptors including bronchodilation and peripheral vasoconstriction (therefore indicated in case 1 with suspected bronchoconstriction and hypotension). Via the same mechanisms adrenaline administration can result in significant tachycardia (in excess of 180 beats per minute), cardiac arrhythmias and hypertension, however these effects are short lived (approximately 5-10 minutes). The adrenaline was diluted by a factor of 10 to allow slower administration, and no adverse drug effects were seen. Case 2 received IV chlorphenamine as first line treatment, which is contradictory to human guidelines, as histamine is one of many inflammatory mediators released in anaphylaxis, and it has no  $\alpha$  or  $\beta$  agonist action unlike adrenaline. Chlorphenamine can cause mild hypotension when administered IV but otherwise causes few adverse effects; therefore risk of iatrogenic harm is low (compared to adrenaline). However once again it is important to stress that although improvement in clinical signs were seen in this case after chlorphenamine, if that had not occurred then it is critical to quickly reassess and change the treatment plan as needed, to avoid valuable time being lost as the patient deteriorates. The difference between this case and the previous is that oxygen saturation remained normal; as if this had not been the case it would have been a trigger for more aggressive therapy to be initiated. The improvement seen in case 2 after chlorphenamine alone could be due to various reasons, the first being possibly a reduced severity of reaction due to the patient not receiving the total prescribed dose. The cefuroxime was also administered at a slower rate in the second case, and through the injection port of the fluid giving set. This could have resulted in the reaction being detected sooner. Early detection therefore may have resulted in chlorphenamine administration limiting further histamine release, and a less severe effect. H1-antihistamines act as inverse agonists, alongside having inhibitory effects on inflammatory cell accumulation (24). Therefore, it may be possible that these anti-inflammatory effects were enough to mitigate the reaction, if it was immunologic as opposed to non-immunologic.

The other adverse event reported in the literature by Gosling (2017) (4) was in a dog enrolled in a study that compared the incidence of adverse reactions to two antibiotics commonly used perioperatively (Zinacef and Augmentin, GlaxoSmithKline). The dog was reported to become mildly hypotensive post cefuroxime administration (systolic arterial blood pressure 88mmHg), which responded to intravenous fluid therapy alone. Prophylactic and perioperative antimicrobial administration is advocated to reduce risk of surgical site infections (SSI's) (25-27). However the cause is often multifactorial and antimicrobial administration is one of many recommendations designed to be implemented together to reduce SSI risk (25), which can be damaging to patient welfare, prognosis and will also increase cost of veterinary treatment (28). Current veterinary guidelines recommend IV perioperative antimicrobial administration within 60 minutes before surgical incision, for procedures expected to last greater than 90 minutes (29). The BSAVA guide to responsible use of antibacterials lists amoxicillin/clavulanate or cefuroxime as agents for surgical use (29). However, neither of these exist in a licenced form for intravenous administration in veterinary patients, therefore must be prescribed under the cascade. In both cases (and as is standard at our institution) the cefuroxime was reconstituted as per the human datasheet, however there are no specific guidelines regarding speed of administration or concentration to be used. Although adverse events of unlicensed medicines can still be reported to the Veterinary Medicines Directorate, this does give potential for under-reporting of adverse events, with no veterinary drug manufacturer to investigate incidence.

#### **LEARNING POINTS/TAKE HOME MESSAGES 3 to 5 bullet points – this is a required field**

- Anaphylaxis can occur after administration of any drug, and can be life threatening.



- Slow administration of drugs can prevent the full dose being given if an adverse reaction is identified early, potentially limiting the severity.
- A crash box with emergency drugs and a quick reference dose chart aids rapid decision-making and treatment (30).
- Reporting of any adverse events to the Veterinary Medicines Directorate (VMD) is key to add to the small amount of veterinary literature in this area.
- Adverse drug events can be reported online via the VMD website:  
<https://www.gov.uk/report-veterinary-medicine-problem>

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**FIGURE/VIDEO CAPTIONS** *figures should NOT be embedded in this document*

Suspected trigger for anaphylaxis	Number of dogs	Reference number
Amoxicillin clavulanate	17	(3),(4)
Cefuroxime	3* (2 cases in this case report)	(4)
Cefazolin	2	(5),(6)
Galidium based contrast	3	(7)
Ionic iodinated contrast	2	(8)
Sodium thiopental	2	(11),(12)
Buprenorphine	1	(9)
Rocuronium	1	(13)

**Table 1: Summary of all reports found relating to specific drug related anaphylaxis in the veterinary literature.**

Sam ple	pH	PaCO <sub>2</sub>	PaO <sub>2</sub>	BE	SpO <sub>2</sub> %	HCO <sub>3</sub>	Na <sup>+</sup>	K <sup>+</sup>	Cl <sup>-</sup>	AnGa p	A-a O <sub>2</sub> gradien t	FiO <sub>2</sub> %
A	7.12	76	237	-9	100	22.6	158	5	11 5	25.7	309.7	90
B	7.16	66	401	- 8. 2	100	21.8	156	3. 9	11 4	24.2	158.2	90
C	7.39	28	114	- 6. 3	98	15.9	159	2. 8	12 2	24	0.7	21

**Table 2: Arterial blood gas results taken from the first case described.**  
**Units: PaCO<sub>2</sub>, PaO<sub>2</sub> and A-a gradient in mmHg; BE, HCO<sub>3</sub>, Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup> and anion gap in mmol/L. A-a O<sub>2</sub> gradient calculated using the alveolar gas equation (31)**

	GA for CT imaging	GA for surgery (adverse event)	GA for surgery, successful
Premedication	Acepromazine, butorphanol	Methadone, dexmedetomidine	Methadone, dexmedetomidine
Induction	Propofol	Propofol	Propofol
Other drugs	Iodinated contrast agent	Cefuroxime, terbutaline*, adrenaline*, dexamethasone*.  *Administered after adverse event	Chlorphenamine, marbofloxacin, atipamizole, Epidural (preservative free morphine and bupivacaine), glycopyrrolate, fentanyl, rocuronium, acepromazine, neostigmine.

**Table 3: Summary of drugs administered to the first described case during three anaesthetics at the hospital.**

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			<b>Anaphylaxis</b>	
Symptom(s)/sign(s) from 1 organ system	Symptom(s)/sign(s) from 2 organ	Lower airway • Mild bronchospasm,	Lower airway • Severe bronchospasm,	Lower or upper airway • Respiratory

<p>present</p> <p><i>Cutaneous</i></p> <ul style="list-style-type: none"> <li>• Urticaria and/or erythema warmth and/or pruritus, other than localized at the injection site</li> </ul> <p>And/or</p> <ul style="list-style-type: none"> <li>• Tingling, or itching of the lips or</li> <li>• Angioedema (not laryngeal)</li> </ul> <p>Or</p> <p><i>Upper respiratory</i></p> <ul style="list-style-type: none"> <li>• Nasal symptoms (e.g., sneezing, rhinorrhea, nasal pruritus, and/or nasal congestion)</li> </ul> <p>And/or</p> <ul style="list-style-type: none"> <li>• Throat-clearing (itchy throat)</li> </ul> <p>And/or</p> <ul style="list-style-type: none"> <li>• Cough not related to bronchospasm</li> </ul> <p>Or</p> <p><i>Conjunctival</i></p> <ul style="list-style-type: none"> <li>• Erythema, pruritus, or tearing</li> </ul> <p>Or</p> <p><i>Other</i></p> <ul style="list-style-type: none"> <li>• Nausea</li> <li>• Metallic taste</li> </ul>	<p>symptoms listed in grade 1</p>	<p>e.g., cough, wheezing, shortness of breath which responds to treatment</p> <p>And/or</p> <p><i>Gastrointestinal</i></p> <ul style="list-style-type: none"> <li>• Abdominal cramps and/or vomiting/diarrhoea</li> </ul> <p><i>Other</i></p> <ul style="list-style-type: none"> <li>• Uterine cramps</li> <li>• Any symptom(s)/sign(s) from grade 1 would be included</li> </ul>	<p>e.g., not responding or worsening in spite of treatment</p> <p>And/or</p> <p><i>Upper airway</i></p> <ul style="list-style-type: none"> <li>• Laryngeal oedema with stridor</li> <li>• Any symptom(s)/sign(s) from grades 1 or 3 would be included</li> </ul>	<p>failure and/or</p> <p><i>Cardiovascular</i></p> <ul style="list-style-type: none"> <li>• Collapse/hypotension†</li> </ul> <p>And/or</p> <ul style="list-style-type: none"> <li>• Loss of consciousness (vasovagal excluded)</li> <li>• Any symptom(s)/sign(s) from grades 1, 3, or 4 would be included</li> </ul>
<p>The final grade of the reaction is not determined until the event is over, regardless of the medication administered to treat the reaction. The final report should include the first symptom(s)/sign(s) and the time of onset after the causative agent exposure and a suffix reflecting if and when epinephrine was or was not administered: a, ≤5 min; b, &gt;5 min to ≤10 min; c, &gt;10 to ≤20 min; d, &gt;20 min; z, epinephrine not administered. Final report: Grade 1-5; a-d, or z; First symptom(s)/sign(s); Time of onset of first symptom(s)/sign(s)</p>				
<p><b>Table 4: Modification of the 2010 WAO grading system (17).</b></p>				

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